

# Hypersensitivity diseases

Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity (Type I)	<p><math>T_H2</math> cells, IgE antibody, mast cells, eosinophils</p>	<p>Mast cell-derived mediators (vasoactive amines, lipid mediators, cytokines)</p> <p>Cytokine-mediated inflammation (eosinophils, neutrophils)</p>
Antibody-mediated diseases (Type II)	<p>IgM, IgG antibodies against cell surface or extracellular matrix antigens</p>	<p>Complement- and Fc receptor-mediated recruitment and activation of leukocytes (neutrophils, macrophages)</p> <p>Opsionization and phagocytosis of cells</p> <p>Abnormalities in cellular function, e.g., hormone receptor signaling</p>
Immune complex-mediated diseases (Type III)	<p>Immune complexes of circulating antigens and IgM or IgG antibodies deposited in vascular basement membrane</p>	<p>Complement and Fc receptor-mediated recruitment and activation of leukocytes</p>
T cell-mediated diseases (Type IV)	<p>1. <math>CD4^+</math> T cells (delayed-type hypersensitivity) 2. <math>CD8^+</math> CTLs (T cell-mediated cytotoxicity)</p>	<p>1. Macrophage activation, cytokine-mediated inflammation</p> <p>2. Direct target cell lysis, cytokine-mediated inflammation</p>

# Type-I Hypersensitivity

# Basic terms

- Type-I = Early= IgE-mediated = Atopic = Anaphylactic type of hypersensitivity
- Atopy = genetic predisposition to type-I hypersensitivity diseases. It is a genetic predisposition to react by IgE production to various stimuli.

# Frequency of atopic diseases

- 20-30% of general population is estimated to be atopic.
- Prevalence of bronchial asthma:
  - General population 5-6%
  - Children: 10%
- Every year 100 people die in Europe of anapylactic shock due to wasp/bee sting.

# Genetic aspects of atopy

- Probability of atopy in a child :
  - Both parents atopics: 80%,
  - One parent atopic: 50%,
  - No parent is atopic: 15%.
- Concordance of asthma in monozygotic twins: only 50-69%

# Candidate genes of atopic diseases

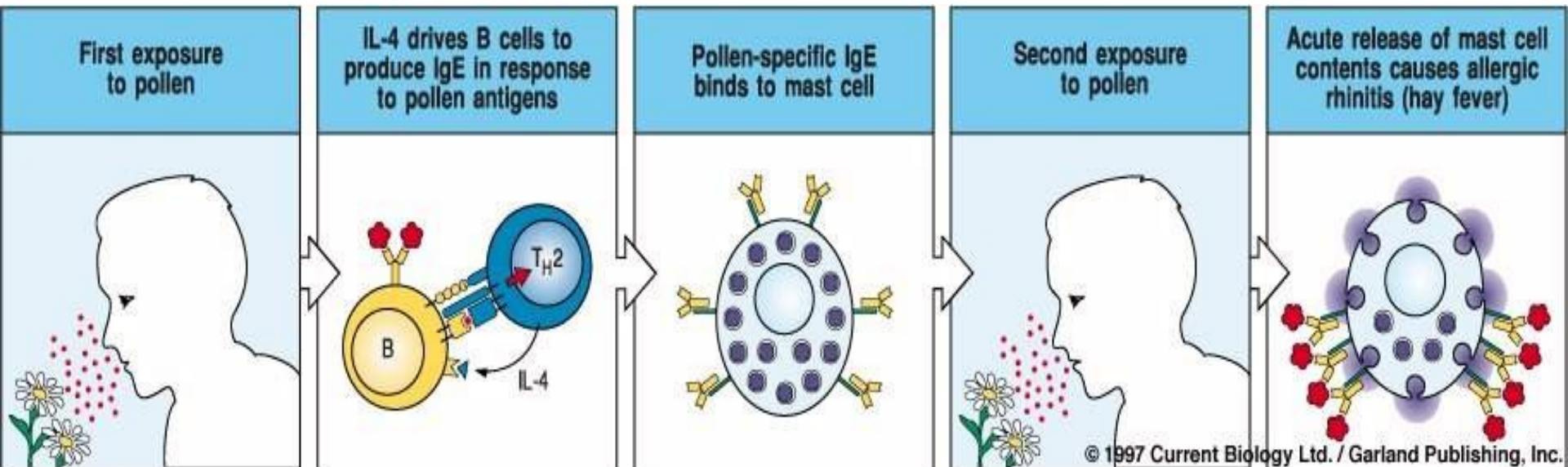
- 5q31-33 : cytokines and their receptors: IL-4, IL-5, IL-9, IL-13
- 11q13: high affinity receptor for IgE
- 6p: HLA genes. TNF- $\alpha$
- 1q, 4q, 7q31, 12q14.3-q24.31, 14q11.2-q13, 16p21, 17q, 19q

# Common allergens

- Pollens (grass, trees)
- House dust mites (*Dermatophagoides pteronyssimus* and *farinae*)
- Foods: nuts, chocolate, shellfish, milk, egg, fruits
- Pets (cat, dog)
- Moulds

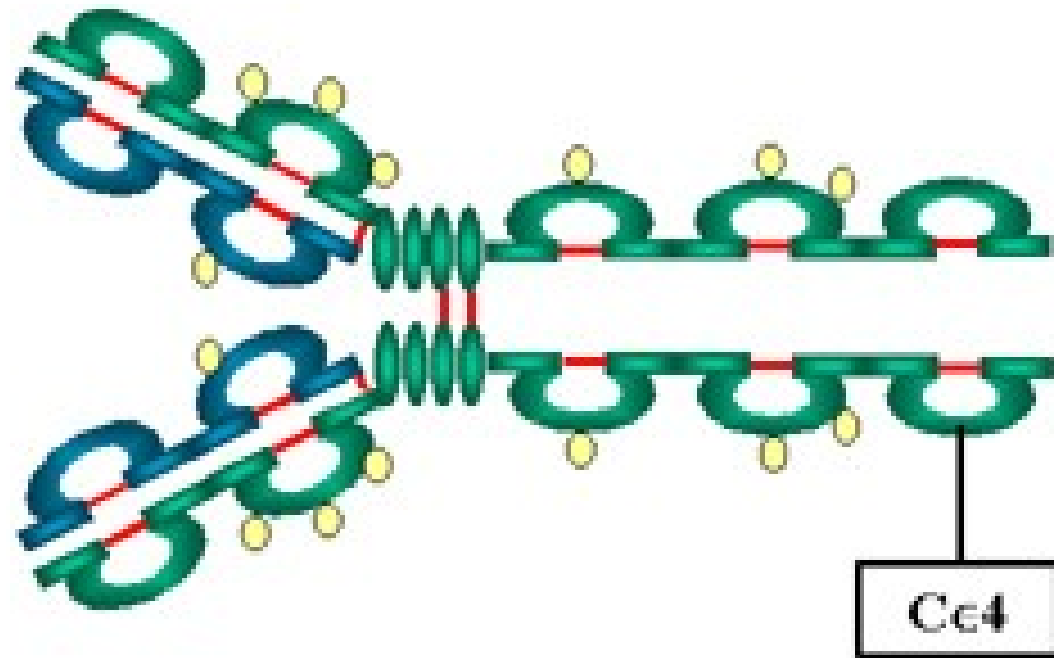


# Type-I hypersensitivity

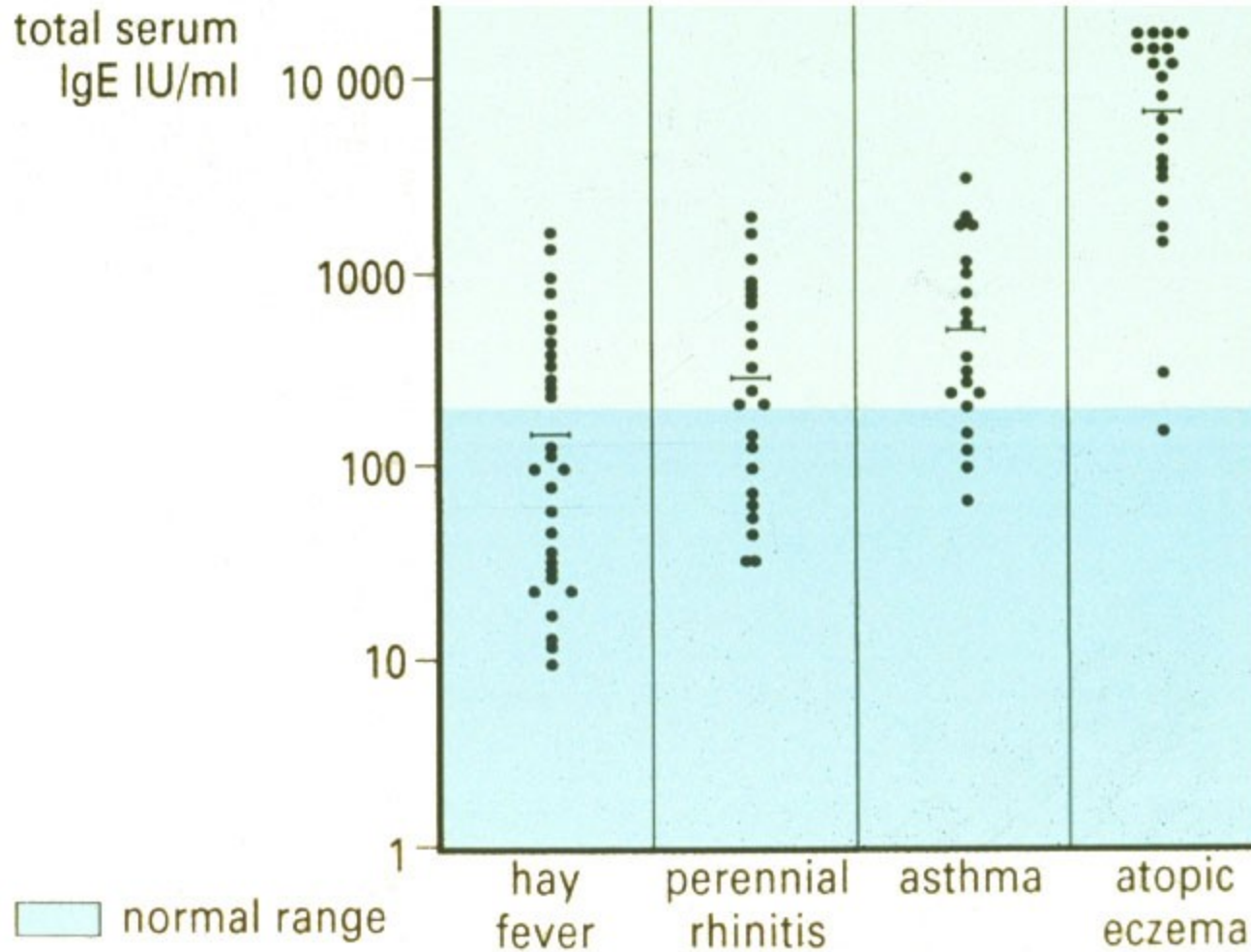


# IgE

- Structure
  - Monomer
  - Extra domain ( $C_{H4}$ )



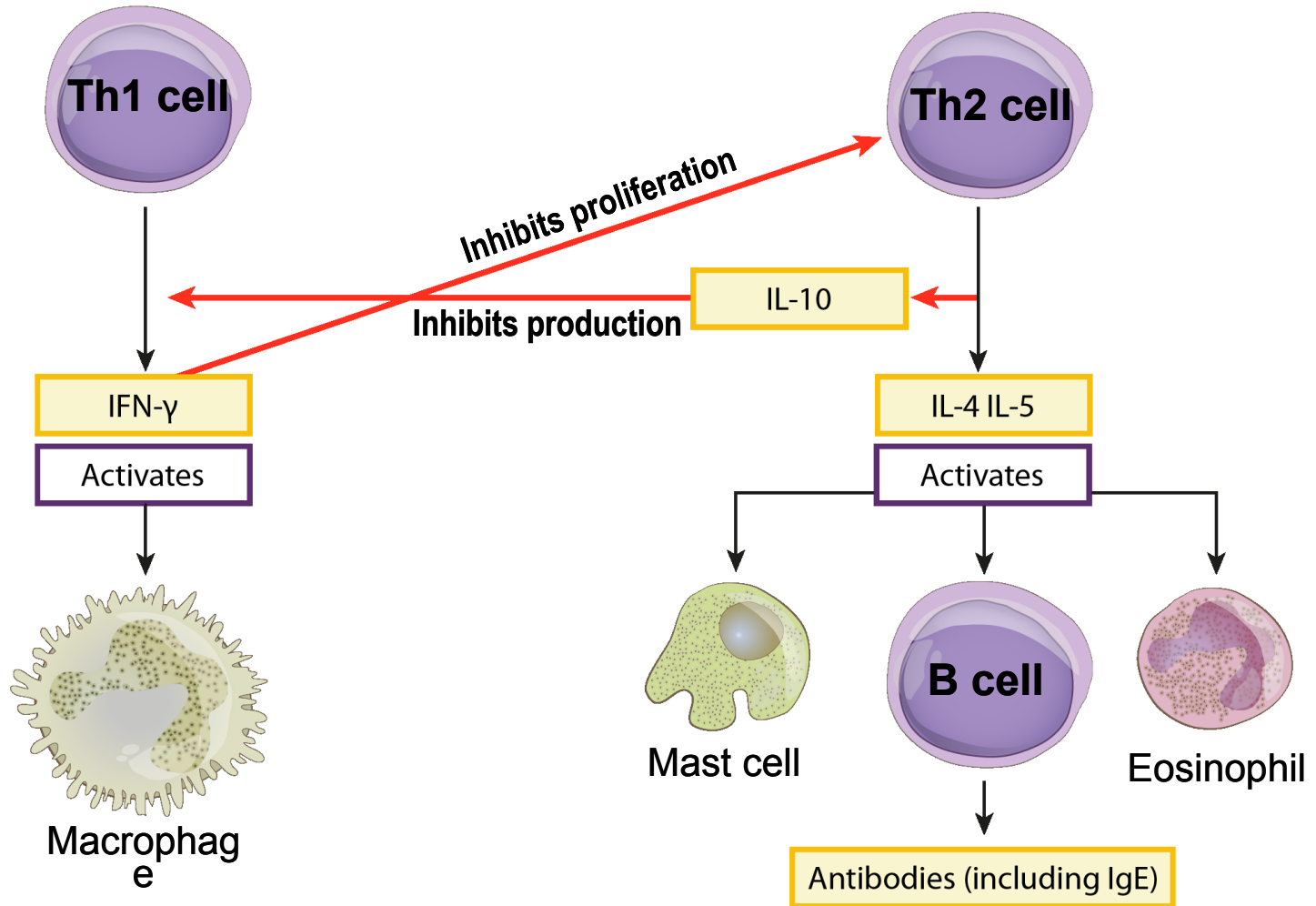
# IgE levels and atopic disease



# Regulation of IgE production

- Positive regulation: IL-4 and IL-13 – products of Th2 cells
- Negative regulation: IFN $\gamma$  - product of Th1 cells

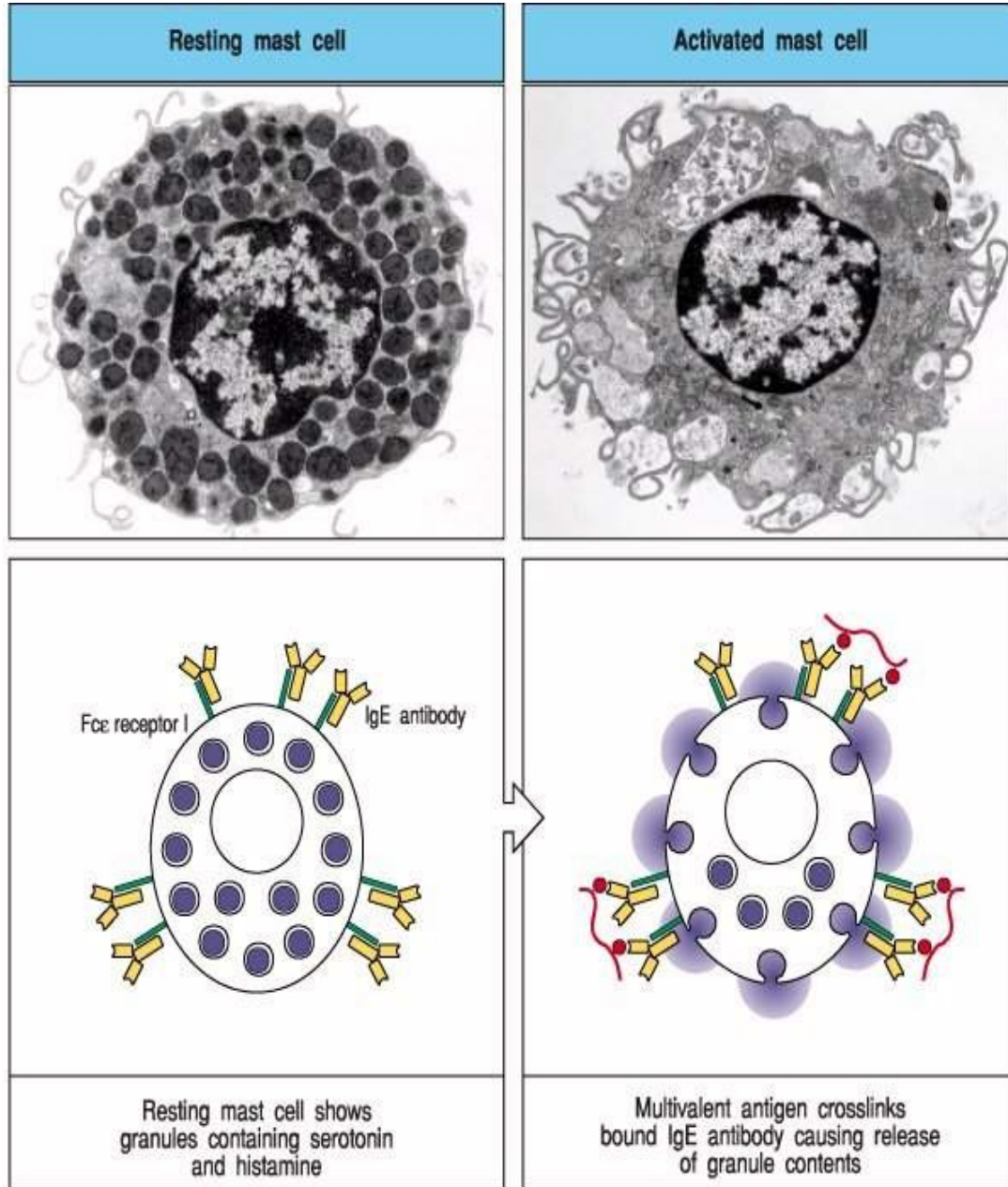
# Functions of Th1 and Th2 cells



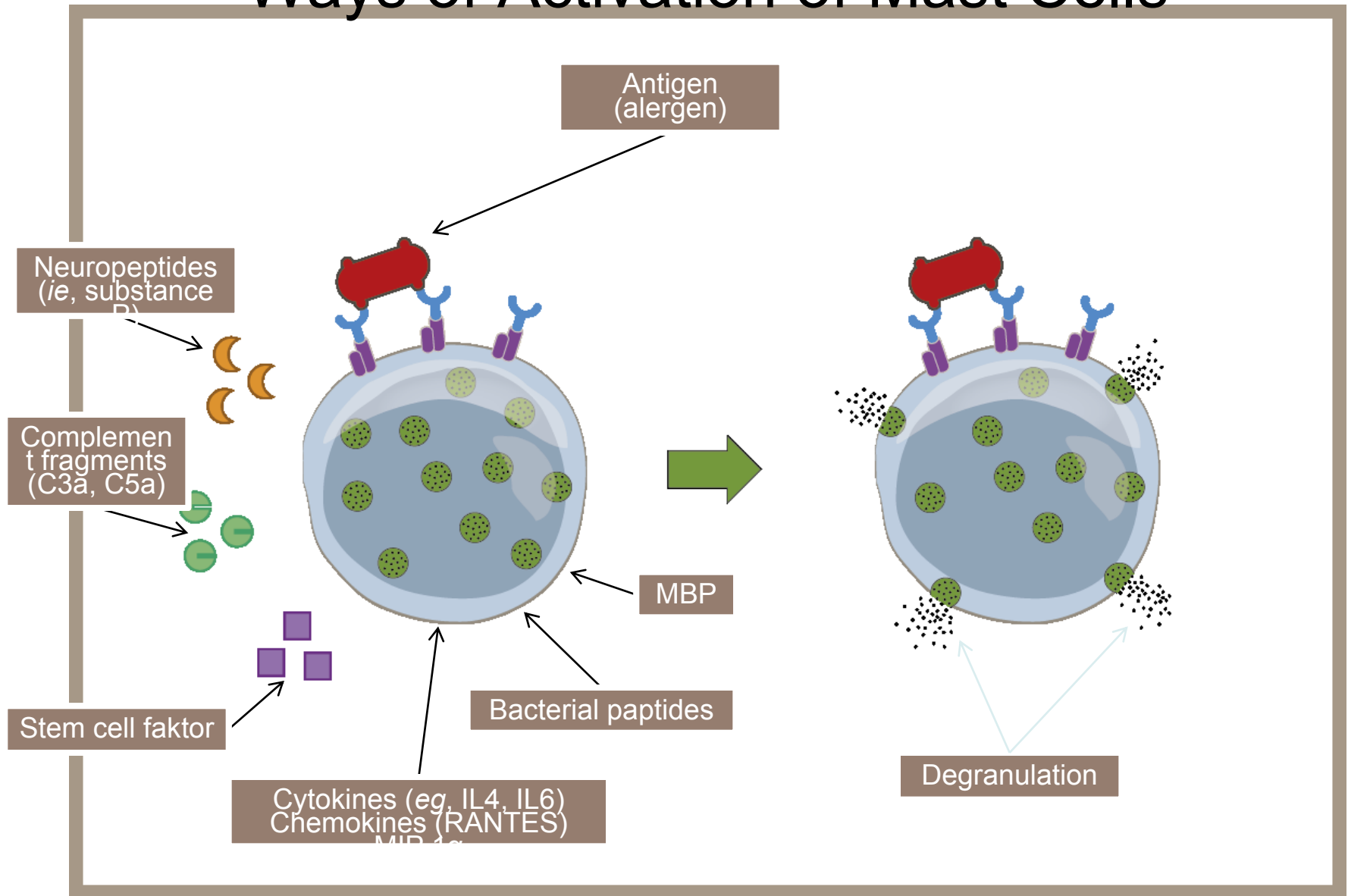
# Mast Cell



# Mast cells



# Ways of Activation of Mast Cells

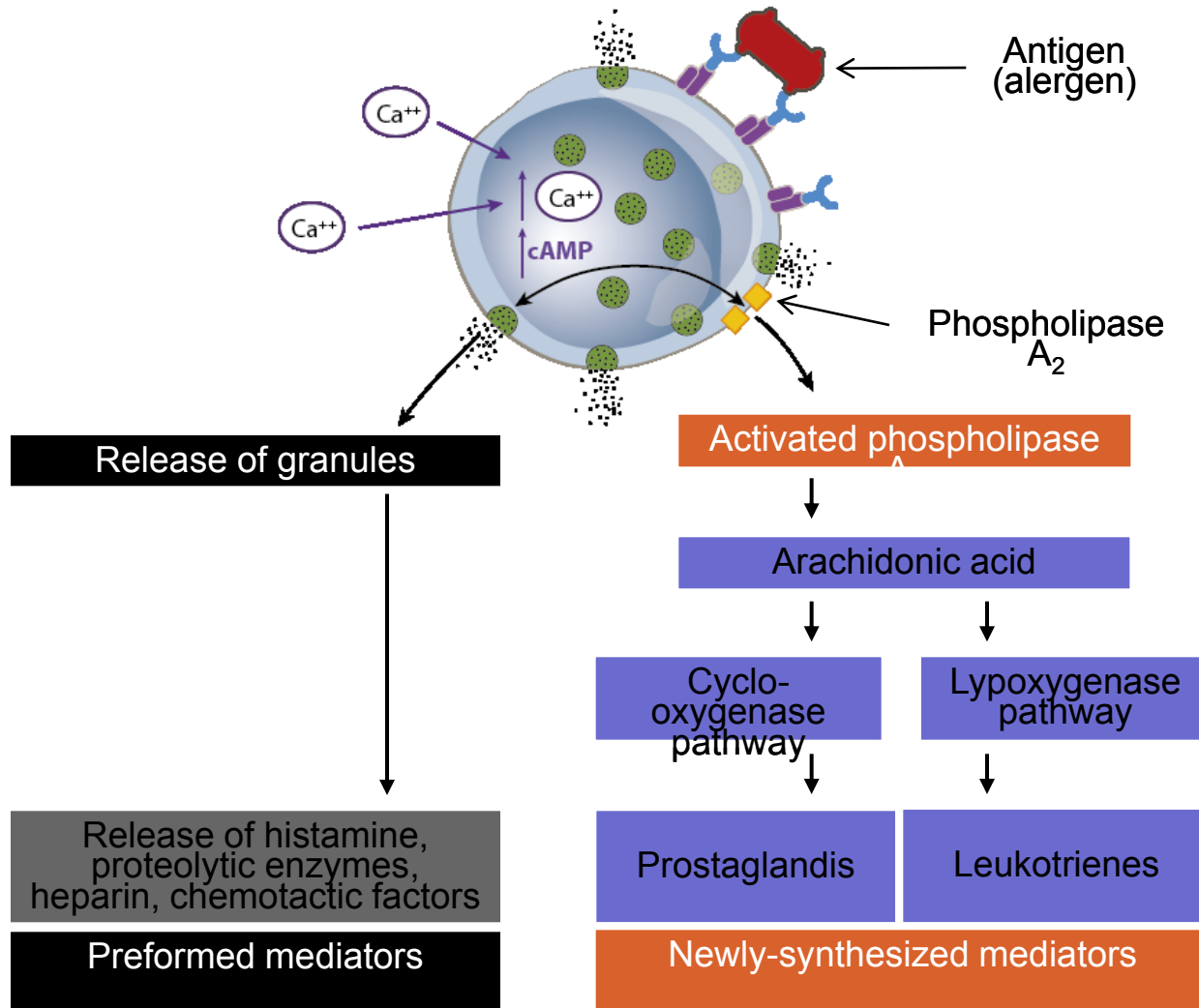




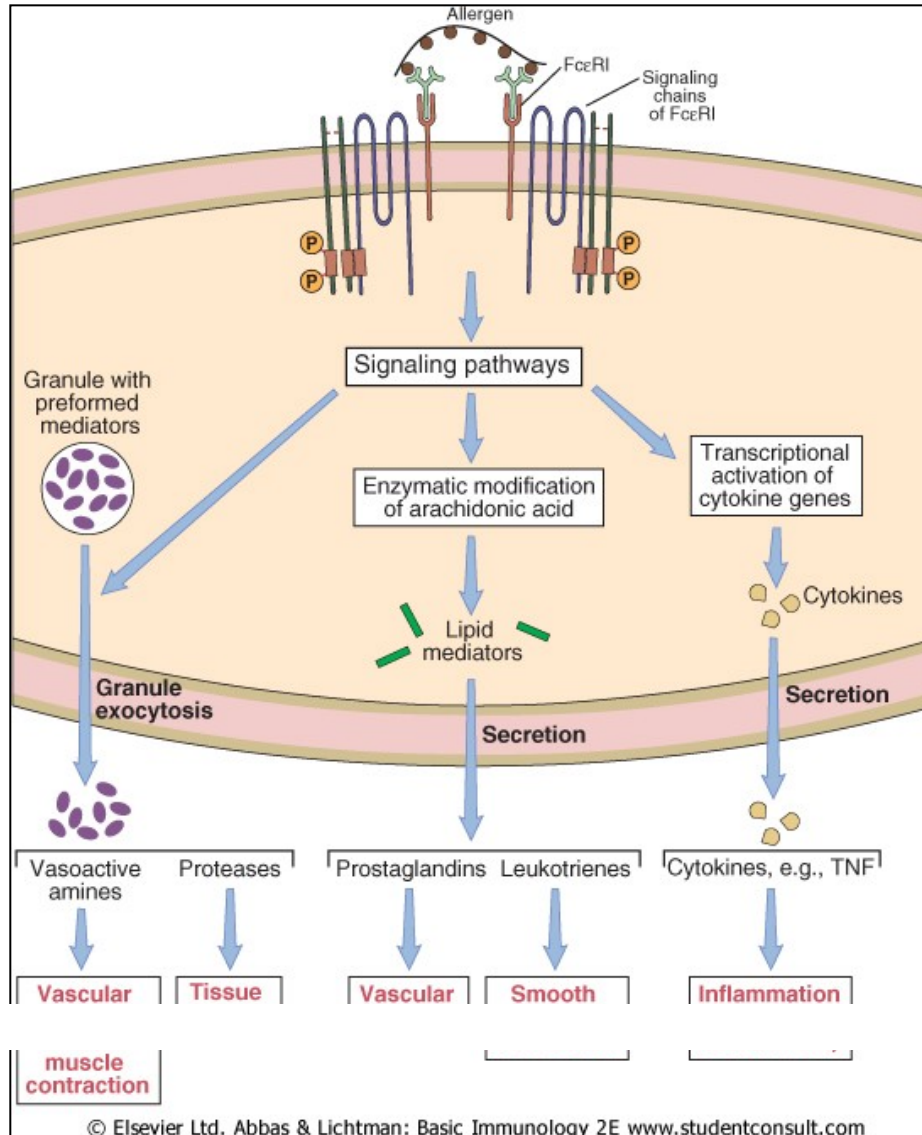
# Biological effects of histamin

- H1: Smooth muscle contraction, increased permeability of capillaries, vasodilatation, increased production of nasal and bronchial secretions, chemotaxis of leukocytes
- H2: increase of gastric juice production, increased production of secretions in respiratory tract
- H3: receptors present in CNS

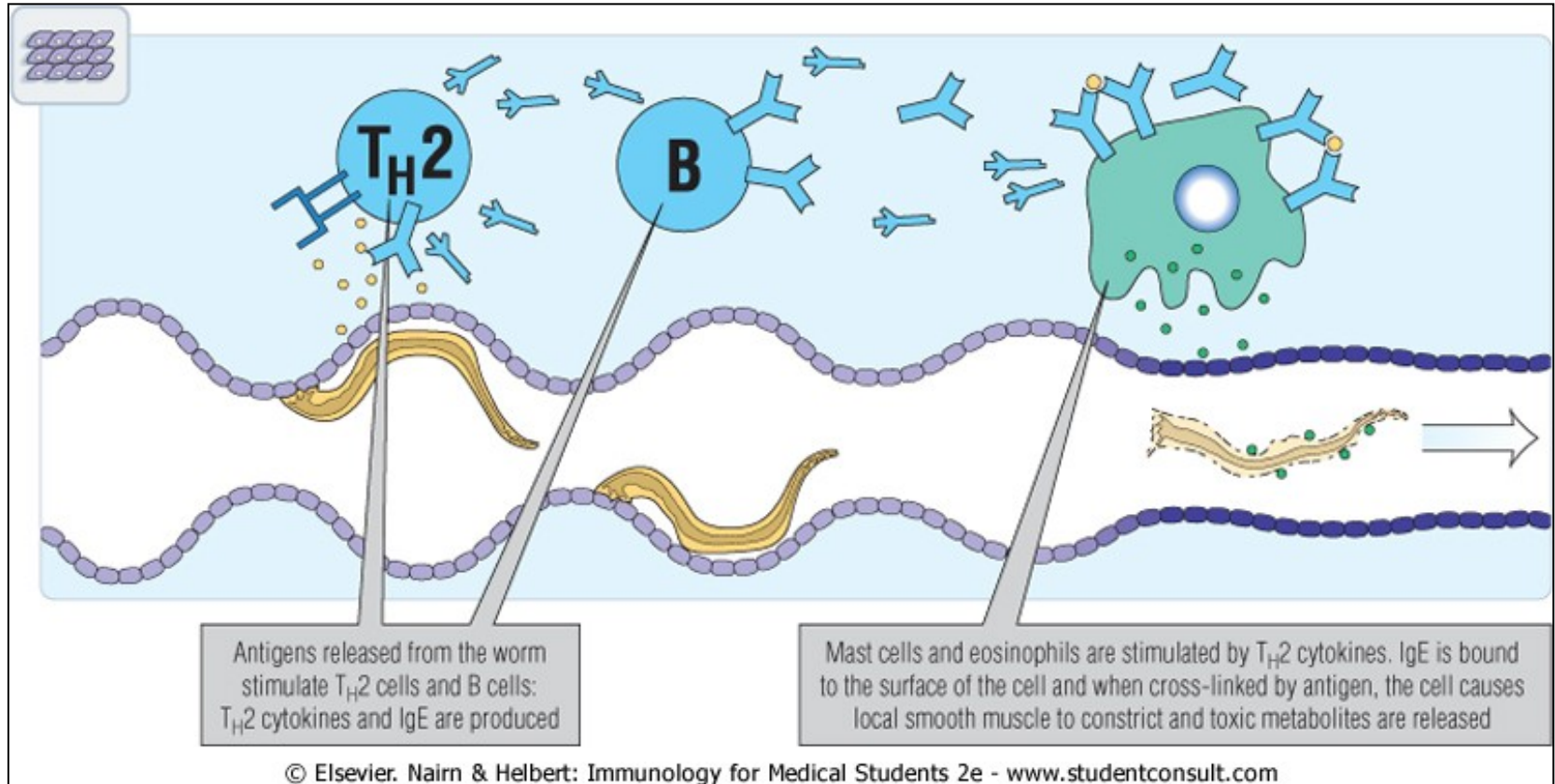
# Consequences of Mast Cell Activation



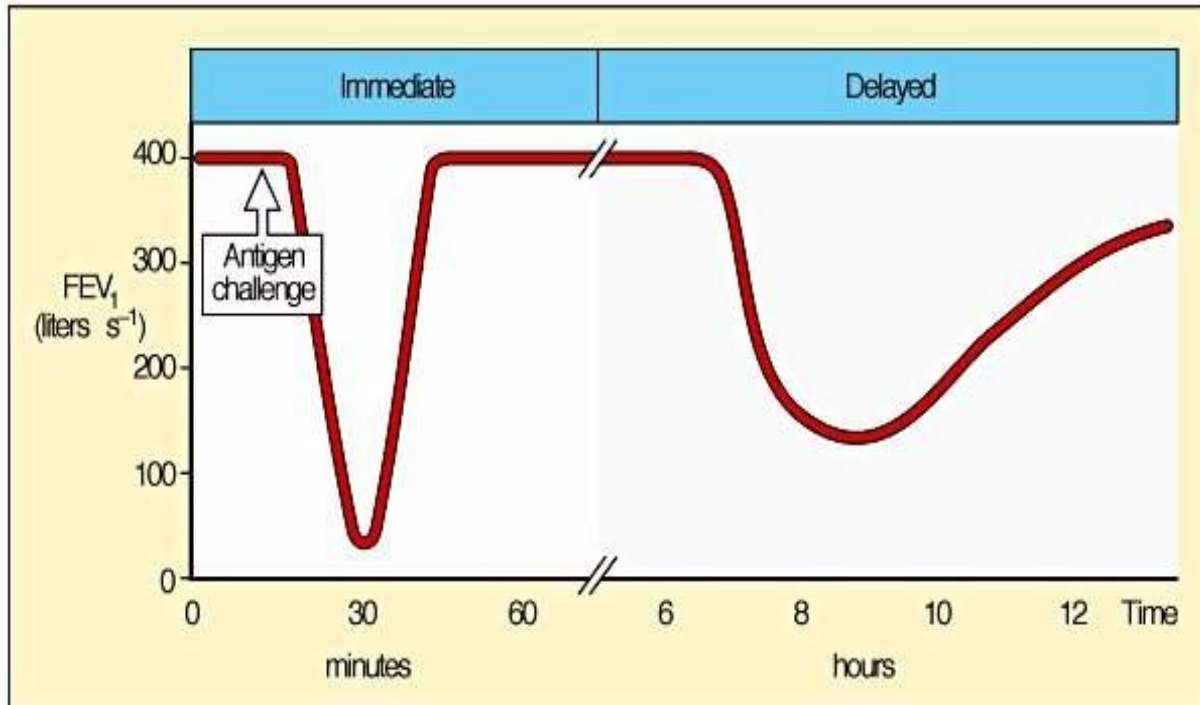
# Consequences of activation of mast cells



# Physiological role of IgE-Mastocyte-Eosinophil system



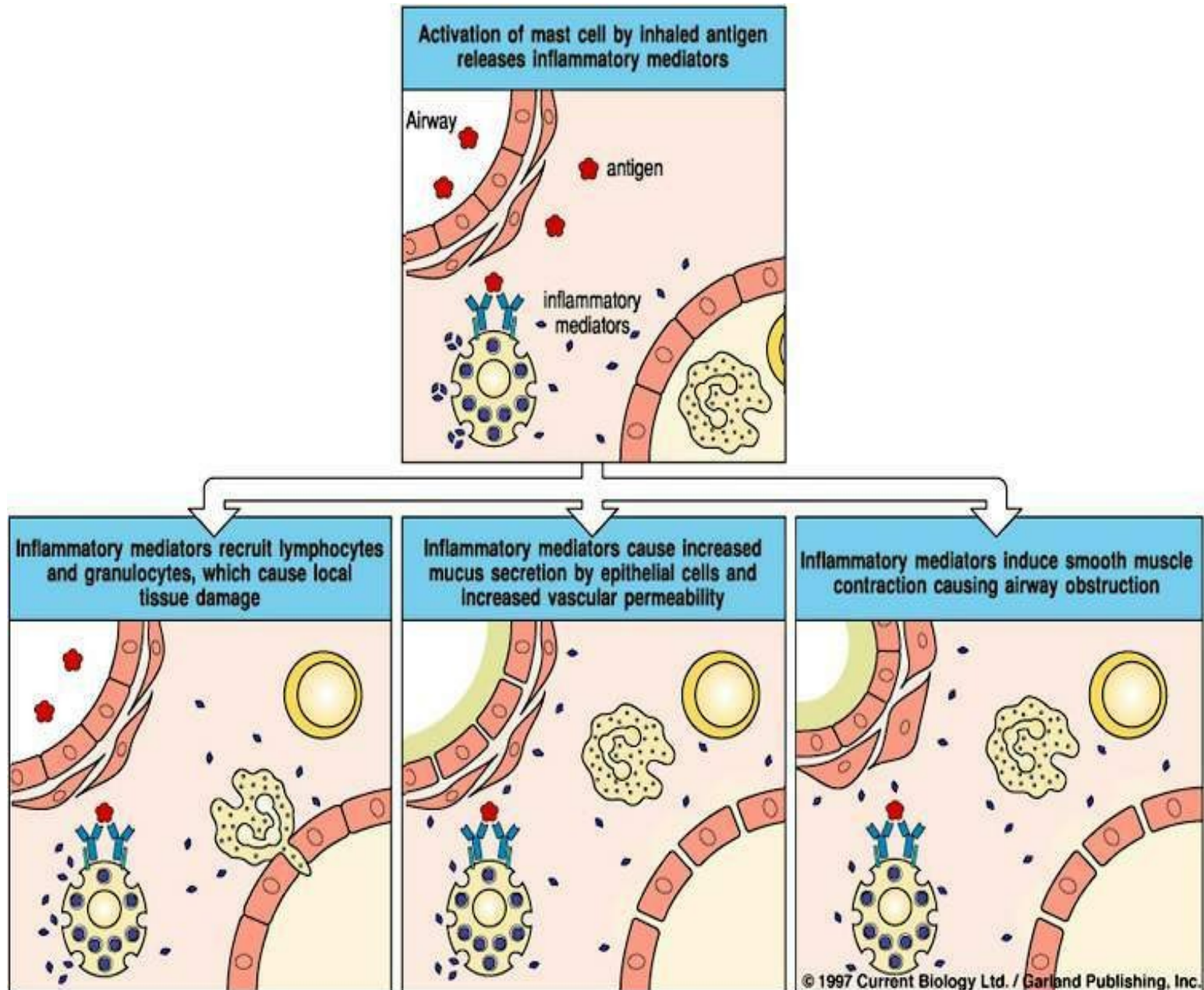
# Immediate and late phase of allergic reaction



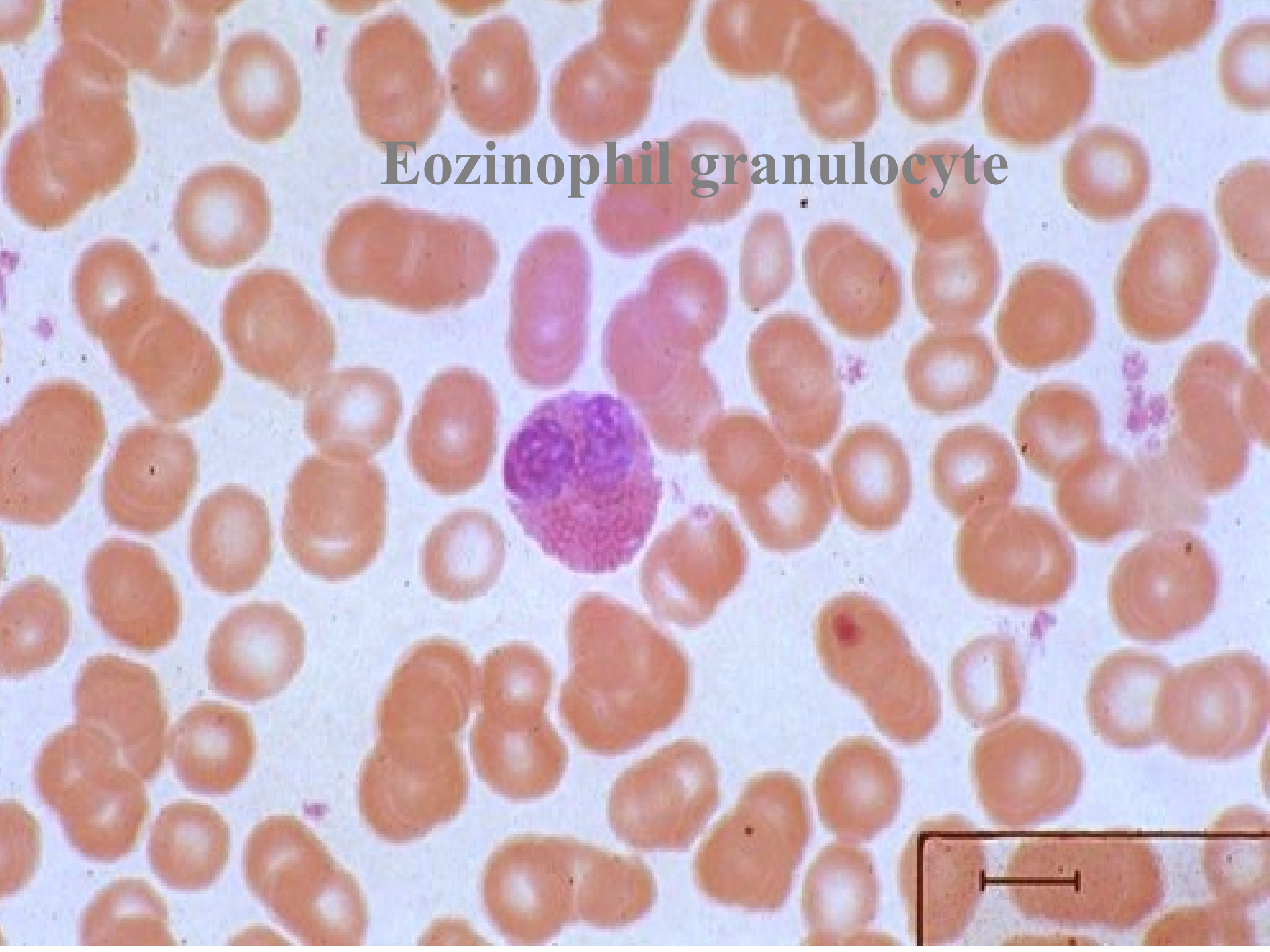
# Phases of type-I hypersensitivity reaction

- Immediate phase – clinical symptoms evolve in several minutes. Mediated mainly by histamin.
- Late phase – symptoms evolve after hours (6-8). Mediated mainly by leukotriens. Presence of eosinophils plays an important role in allergic inflammation.

# Allergic reaction in bronchi



# Eozinophil granulocyte

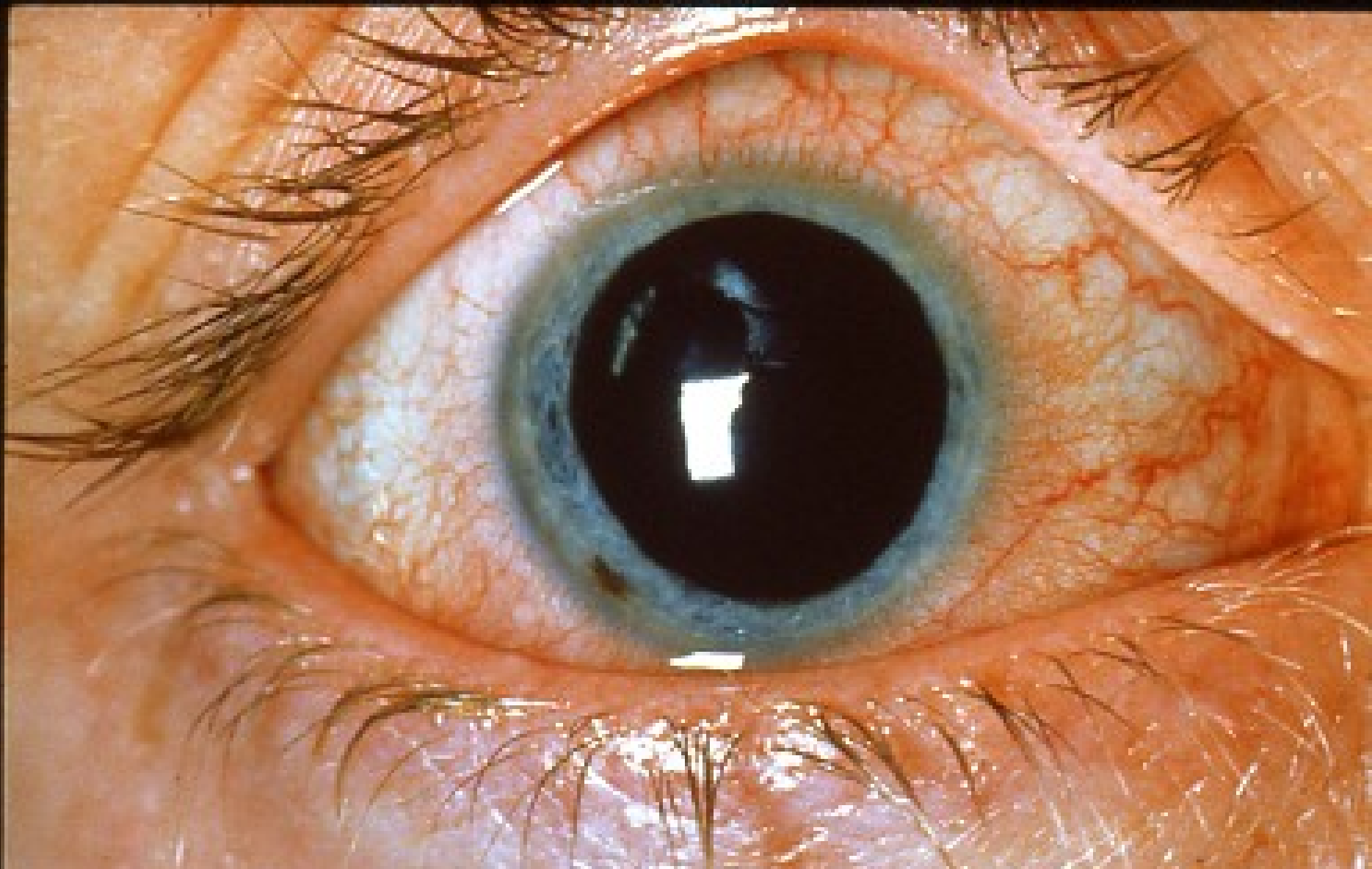




# Clinical diseases caused by atopic hypersensitivity

- Allergic conjunctivitis
- Allergic rhinitis
- Bronchial asthma
- Allergy of gastrointestinal tract
- Urticaria and angioedema
- Atopic eczema
- Anaphylactic shock

# Allergic conjunctivitis



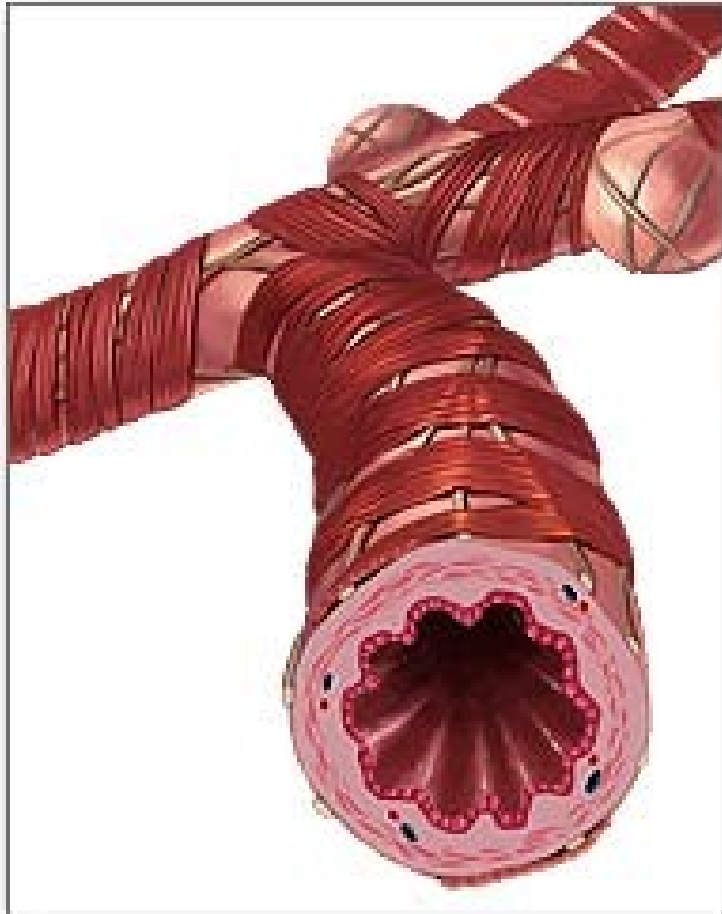
# Allergic rhinitis



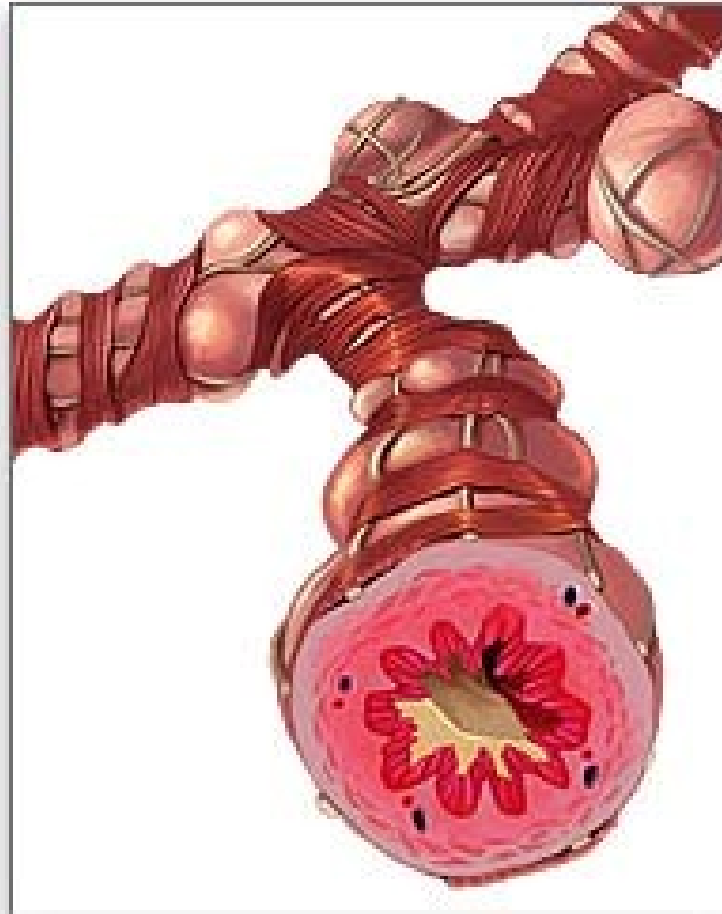


# Bronchial asthma

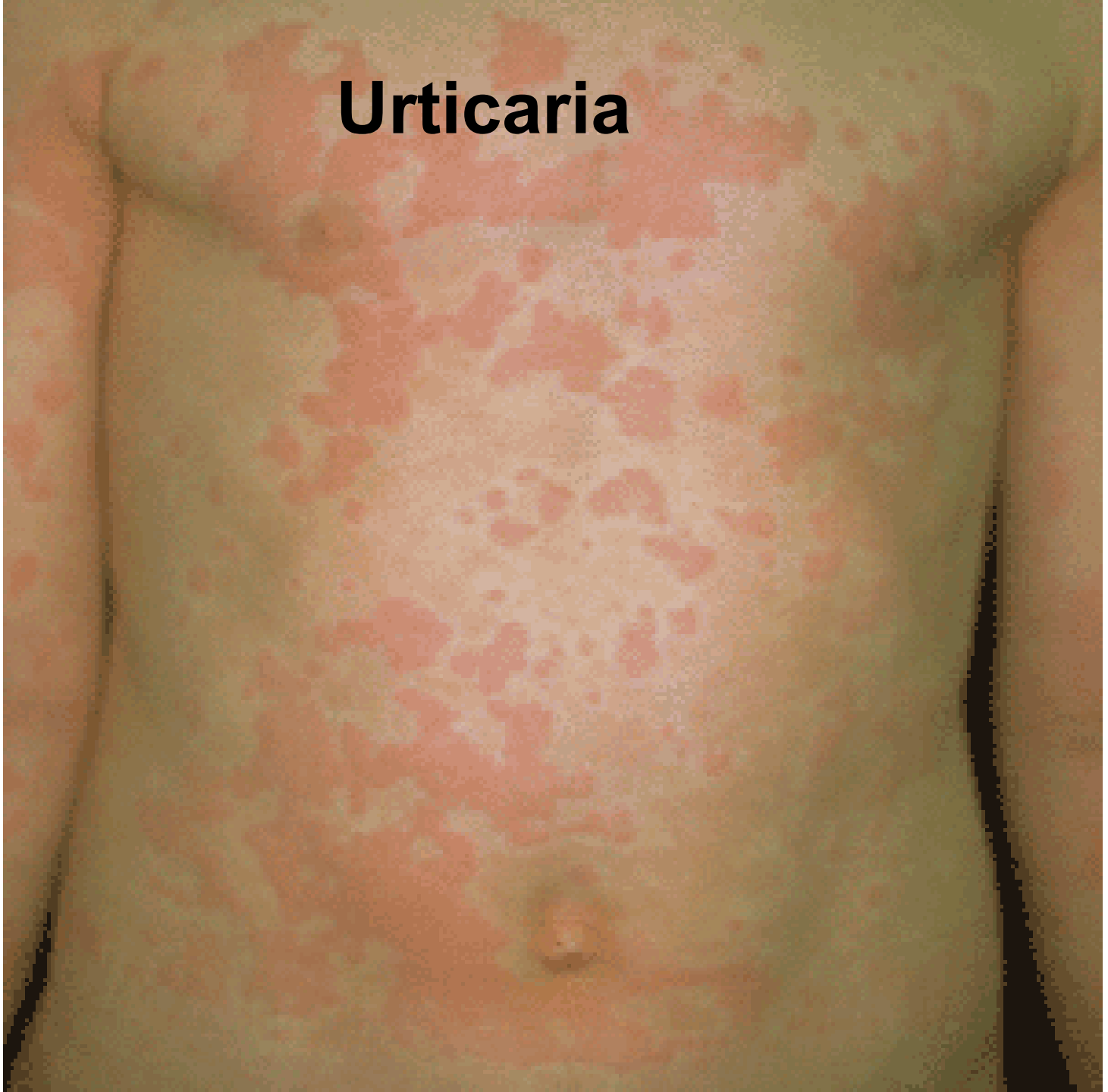
Normal bronchiole



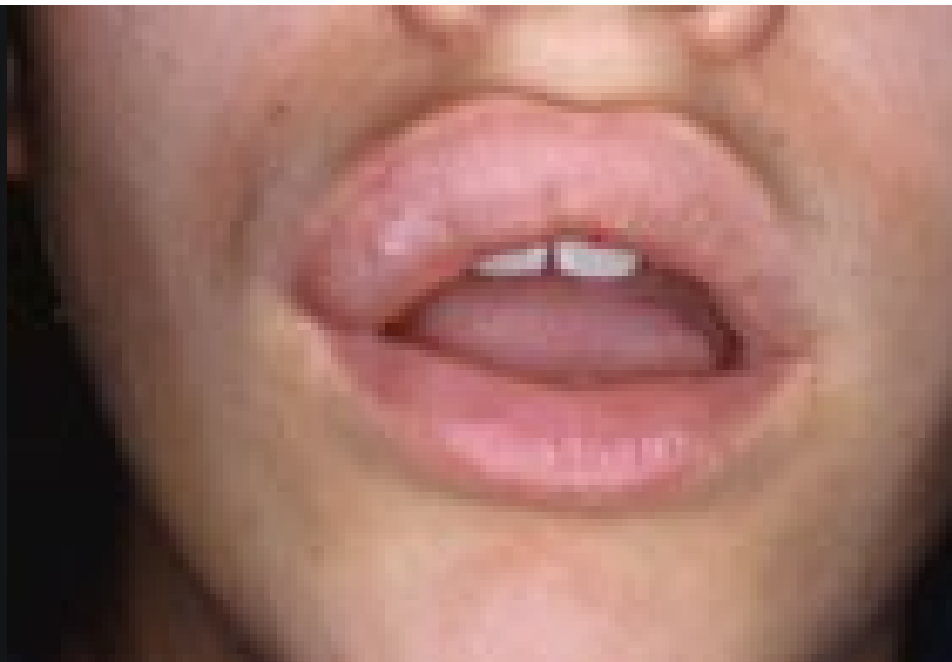
Asthmatic bronchiole



# Urticaria



# Angioedema



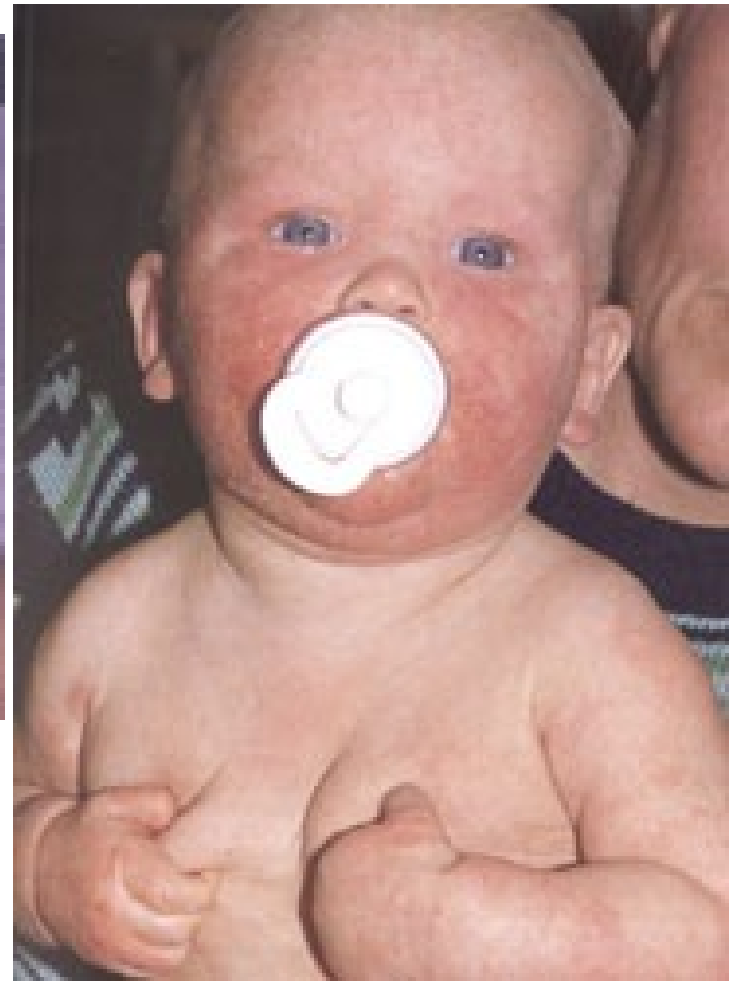


*Facial angioedema following allergen exposure (A) and resolution after treatment (B).*

Reprinted from Tharp M, Levine M, Fireman P Urticaria and angioedema. In: Fireman P, Slavin R (eds). Atlas of Allergies. 2nd ed. London: Mosby-Wolfe; 1996: 250. By permission of the publisher Mosby.



# Atopic eczema



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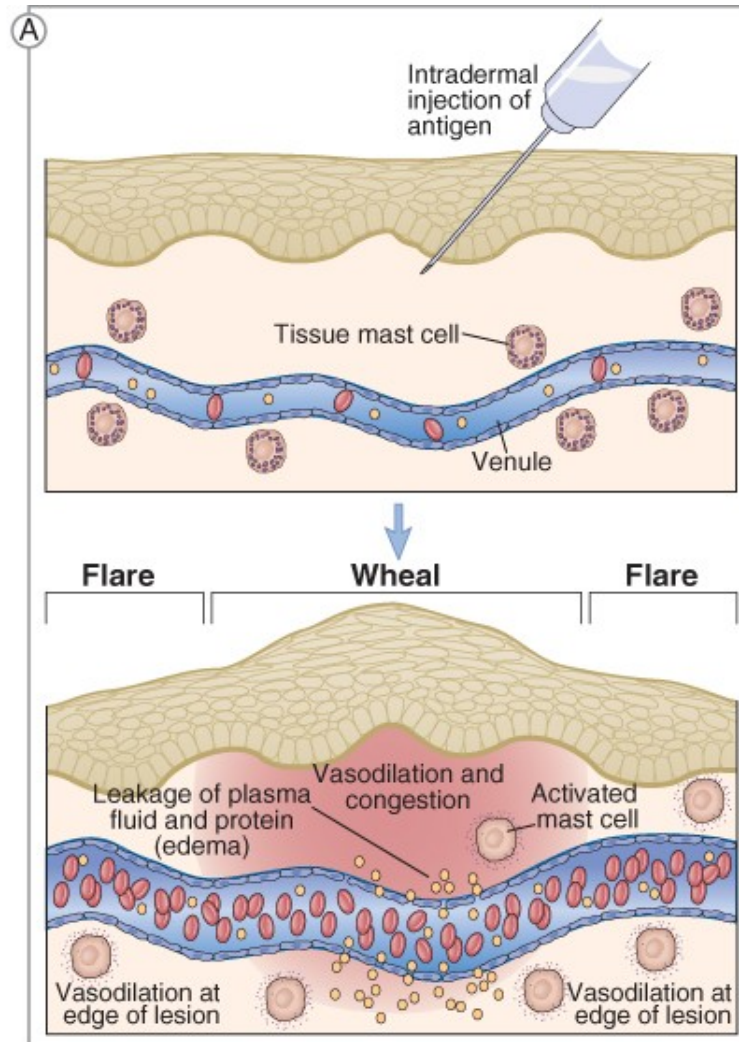
# Treatment of allergic diseases

- Allergen avoidance
- Antihistaminics
- Topical or systemic corticosteroids
- Antilekotriens
- Cromons (cromolyn sodium, nedocromil) - stabilise membrane of the mast cells
- In asthma:  $\beta$ -2 agonists, xantins
- Allergen immunotherapy (desensitisation)

# Diagnostic approaches in type-I hypersensitivity

- Past history
- Eosinophilia
- Skin tests
- Provocation and elimination tests

# Intradermal allergy test



# Skin prick tests



CONT. )

H. DUST )

MITTE )

GRASS )

SHRUB )

TREE )



# Causes of anaphylactic shock

- Drugs - penicillins, cephalosporins, proteolytic enzymes, local anesthetics
- Food - nuts, seafood, chocolate
- Allergen desensitisation, allergen skin tests
- Bee or wasp sting
- X-ray contrast media

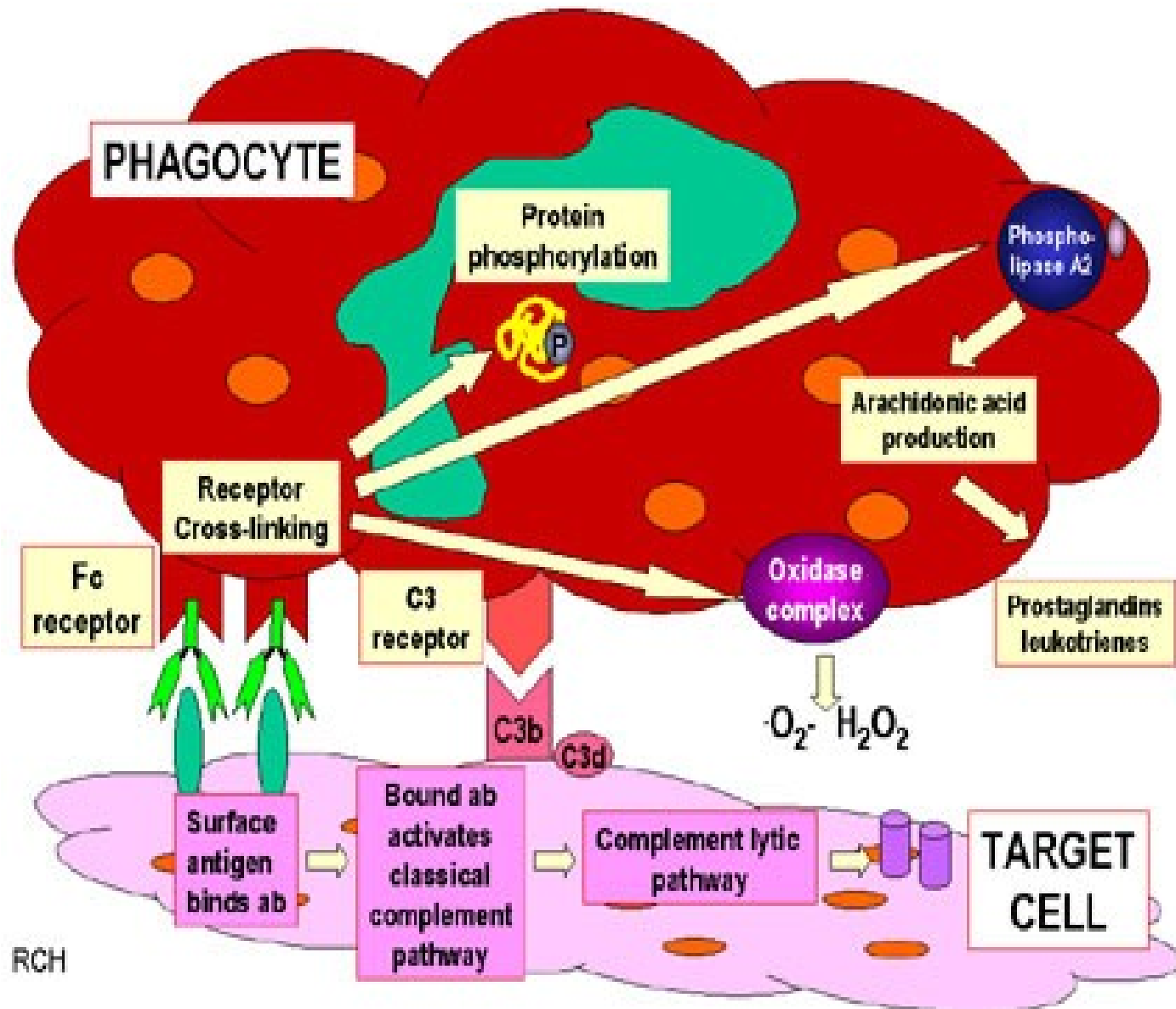
# Clinical symptoms of anaphylactic shock

- Hypotension (systolic pressure 90 mm Hg or less)
- Tachykardia
- Dyspnea
- Abdominal pain, nausea
- Anxiety
- Urticaria on the skin, sweating, itching
- Contractions of the uterus

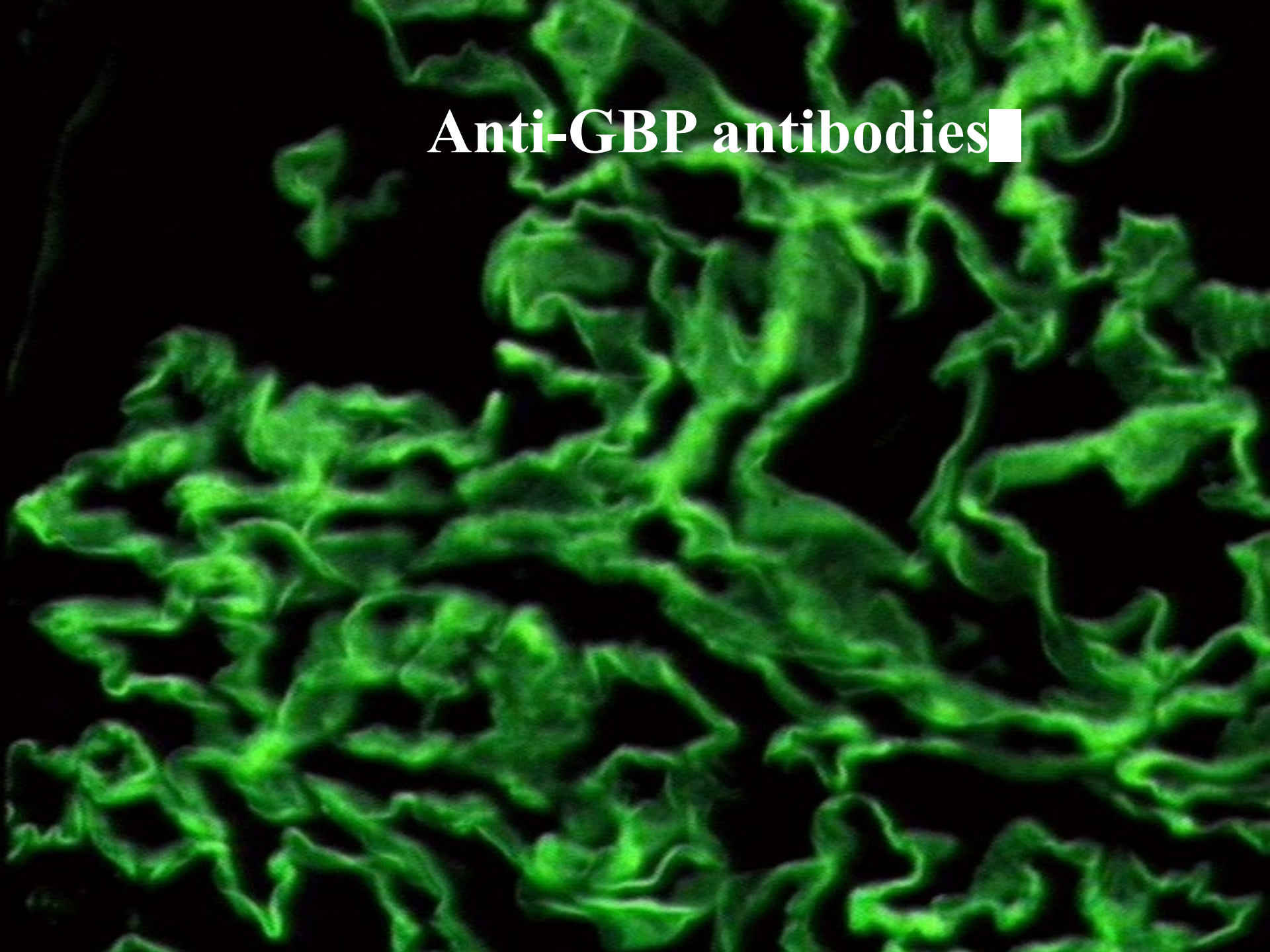
# Treatment of anaphylactic shock

- Adrenalin intravenously or intramuscularly 10 µg/kg repeatedly
- Antihistaminics intravenously
- Syntophyllin 240 mg intravenously or inhalation of β-2-mimetics
- Corticosteroids ( 200-500 mg of hydrocortisone) intravenously
- Oxygen
- Vasopressor agents (dopamin or noradrenalin)

# Type-II hypersensitivity



**Anti-GBP antibodies** ■



# Diseases caused by immune complexes deposition

- Caused by a disturbed transport or metabolism of immune complexes.
- They usually deposit in the wall of vessels (causing vasculitis) or glomeruli (causing glomerulonephritis), less frequently in the place of their formation (extrinsic alveolitis).
- The most important laboratory test is the direct immunofluorescence to detect the IgG part of the complexes.

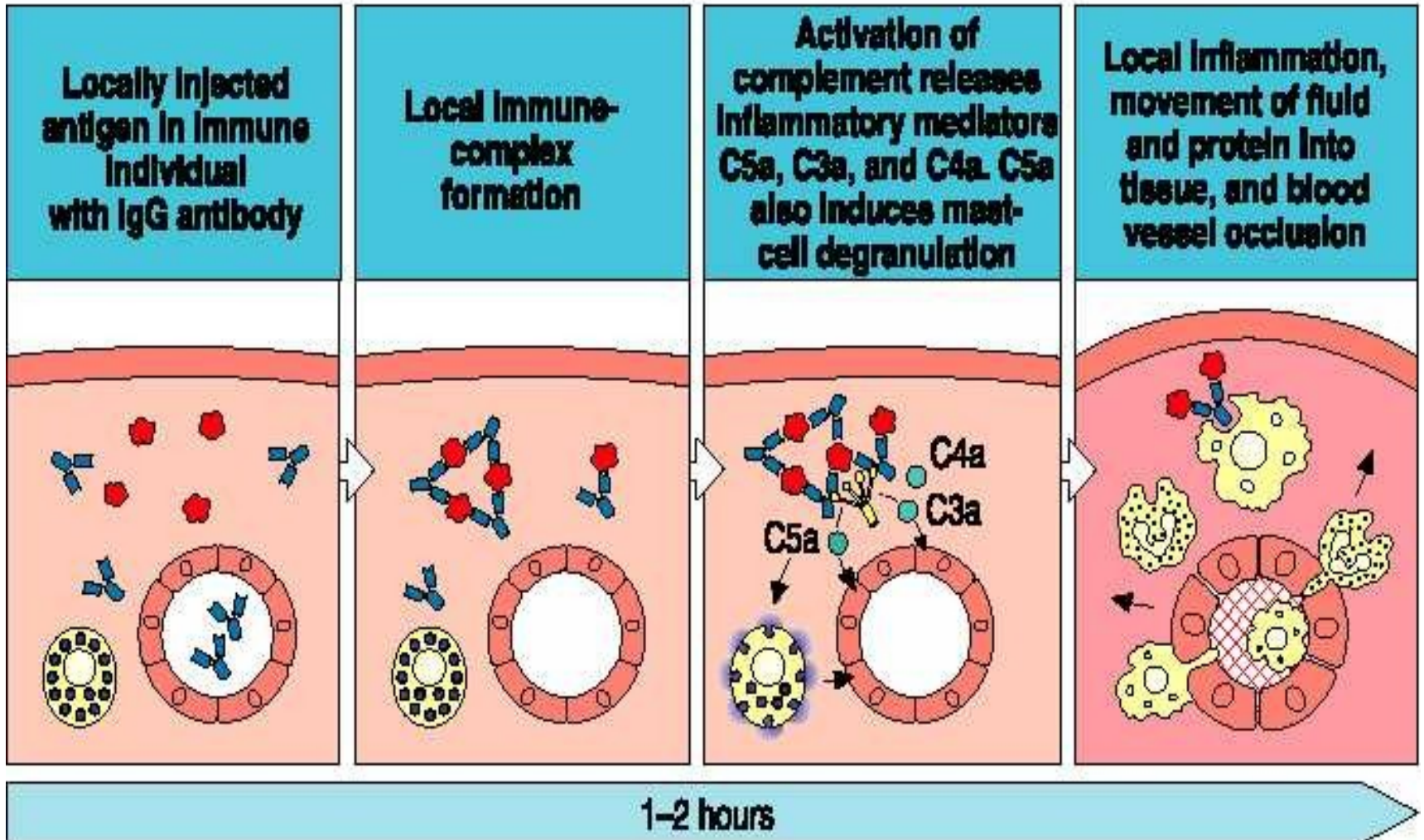
# Immunocomplex diseases

## (type III immunopathological reaction)

- Caused by deposition of immune complexes in places different from their normal metabolism.
- In case of circulating immune complexes (small, soluble complexes with excess of antigen), they deposit mainly in blood vessels walls and glomeruli leading to vasculitis and/or glomerulonephritis.
- Less frequent is the situation when immune complexes deposit in the place of their formation (large complexes with excess of antibodies). They deposit in the place of their formation.
- By activation of the complement system and phagocytoc cells they induce local inflammation.

# Type III hypersensitivity

Figure 10.29

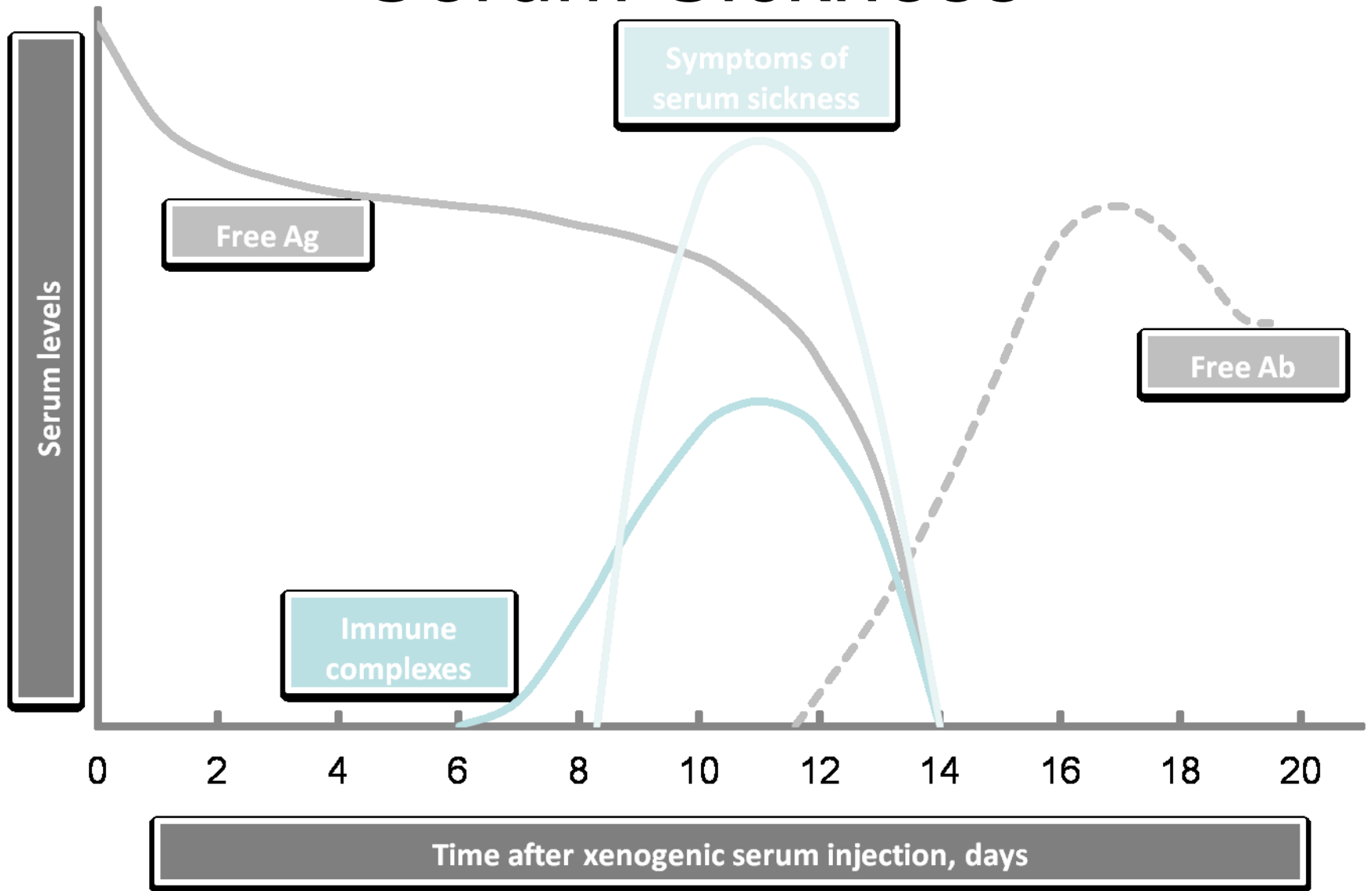




# Serum sickness

- Manifests 8-12 days after the uses of xenogenic serum.
- Urticaria, fever, arthralgia, lymphadenopathy
- Albuminuria
- Deposits of immunocomplexes in vessels.
- Self-limiting disease, in case of need steroids or antihistaminics can be used.

# Serum Sickness



# Extrinsic alveolitis

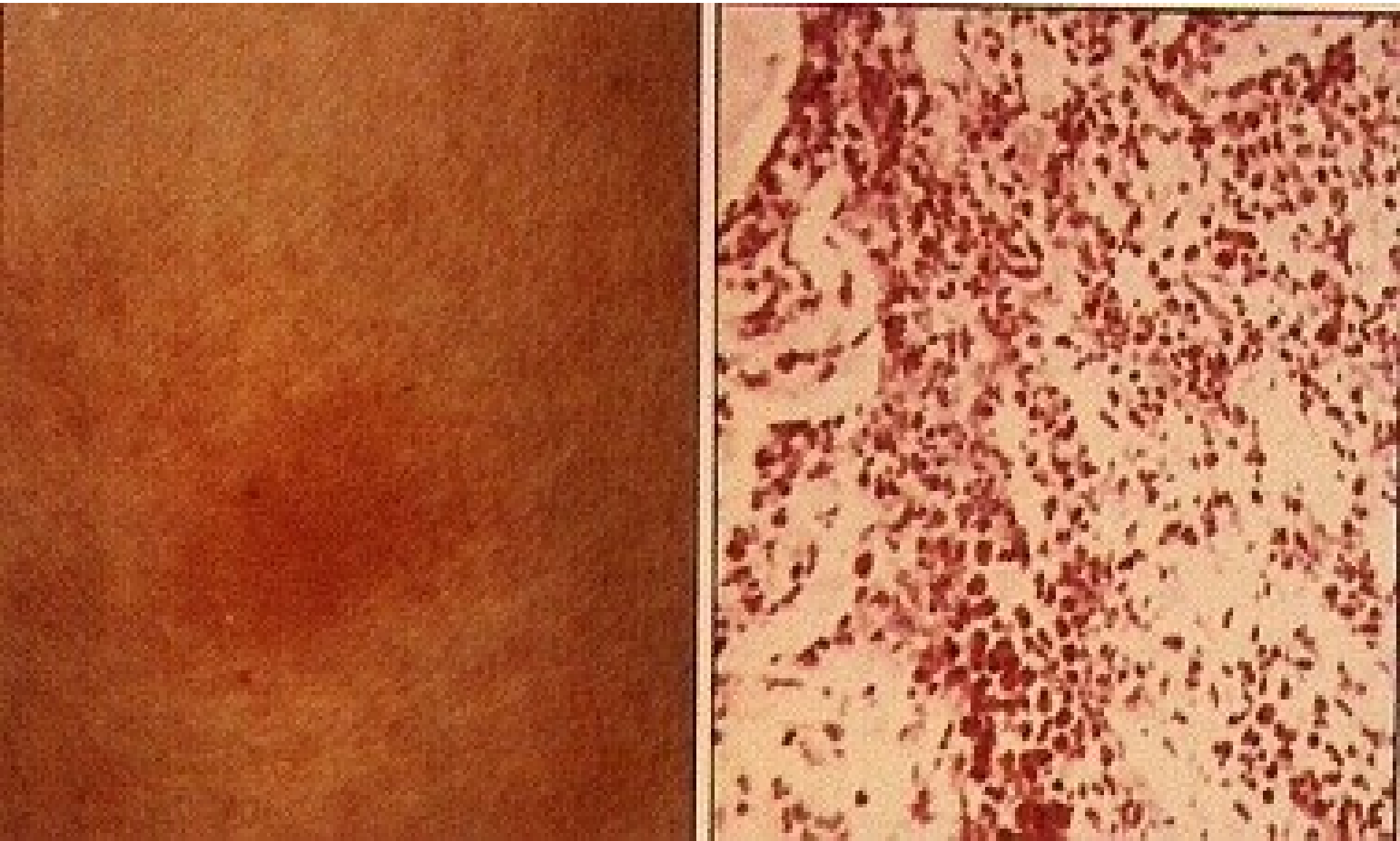
- Caused by deposition of insoluble immune complexes in the lung tissue. The complexes are formed from exogenous antigen and excess of antibodies of IgG class.
- 6-8 hours after exposition the patient suffers from dry cough, dyspnea, increased body temperature, lymphadenopathy.
- Repeated exposures lead to lung fibrosis..
- Most frequently caused by bird antigens (pigeons – pigeon breeder's disease, parrots), thermophil actinomycetes (farmers' lungs disease).

# Administering the Tuberculin Skin Test

- Inject intradermally 0.1 ml of 5 TU PPD tuberculin
- Produce wheal 6 mm to 10 mm in diameter
- Do not recap, bend, or break needles, or remove needles from syringes
- Follow universal precautions for infection control



# Tuberculin reaction



# Examples of diseases where type-IV hypersensitivity plays a key role

- Contact exzema
- Cavitation in tuberculosis
- Sarcoidosis
- Several types of vasculitis
- Autoimmune diseases where T-lymphocytes play a major role ( multiple sclerosis)

# Contact dermatitis due to nickel hypersensitivity



Allergy Capital: *Contact dermatitis*. Australian Allergy, Asthma and Immunology Information.  
[http://www.allergycapital.com.au/allergycapital/Contact\\_dermatitis.html](http://www.allergycapital.com.au/allergycapital/Contact_dermatitis.html)

# Contact dermatitis

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